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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/760,362	CHEN, JAMES C.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,11,12,16-24,36 and 38-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 11-12, 16-24, 36, and 38-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8/25/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 19, 11-12, 16-24, 36, and 38-41 are pending and are being acted upon.

2. The traversal of the restriction filed 8/25/03 is acknowledged. The traversal is on the grounds that each claims 1-6, 11, 12, 16-24 and 36 is directed to a generic method for treating neovascular disease. There are no reasons of record to establish that the generic claims should not be examined along with the elected group. If the linking claims are deemed allowable, then the restriction requirement must be withdrawn and all claims directed to nonelected subject matter must be fully examined for patentability. For the record, generic claims 1, and 36 have been examined along with the elected group that read on the specific photosensitizer chlorin and the specific antibody to VEGF receptor. Until the generic linking claims are deemed allowable, the

3. The following new grounds of rejections are necessitated by the amendment filed 8/25/03.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-6, 11-12, 16-24, 36, and 38-41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method to treat neovascular disease of the eye comprising the method steps of (a) administering a verteporfin conjugated anti-ED-B of fibronectin antibody that selectively binds to abnormal endothelium that lines or composes neovascular tissue to a subject, (b) allowing non-specifically bound photosensitizing compound to clear from collateral tissues, (c) illuminating the neovascular tissue with light for a period of time sufficient to activate said photosensitizing compound thereby causing damage to neovascular tissue, but without impairing or destroying other tissue, wherein the subject is irradiated in or more sessions for a total period of 10 minutes with 400 mW/cm^2 of colliminated LED light having a wavelength of 690nm for a total fluence of 240 $Joules/cm^2$, (2) a method to treat neovascular disease of the eye comprising the method steps of (a) administering a benzoporphyrin derivative conjugated to VEGF to a subject, (b) allowing non-specifically bound photosensitizing compound to clear from collateral tissues, (c) illuminating the neovascular tissue

with light for a period of time sufficient to activate said photosensitizing compound thereby causing damage to neovascular tissue, but without impairing or destroying other tissue, wherein the subject is irradiated in one or more sessions for about 20 minutes with no more than 500 mW/cm^2 for a total fluence of illumination of about 600 $Joules/cm^2$, (3) a method to treat neovascular disease of the eye comprising the method steps of (a) administering a benzoporphyrin conjugated to anti-CEA antibody that selectively binds to abnormal endothelium that lines or composes neovascular tissue to a subject, (b) allowing non-specifically bound photosensitizing compound to clear from collateral tissues, (c) illuminating the neovascular tissue with light for a period of time sufficient to activate said photosensitizing compound thereby causing damage to neovascular tissue, but without impairing or destroying other tissue, wherein the subject is irradiated in or more sessions for approximately 1 hour with a radiant exposure of 250 mW/cm^2 for a total fluence of 900 $Joules/cm^2$, **does not** reasonably provide enablement for a method to treat neovascular disease of the eye as set forth in claims 19, 11-12, 16-24, 36, and 38-41. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only (1) a method to treat neovascular disease of the eye comprising the method steps of (a) administering a verteporfin conjugated anti-ED-B of fibronectin antibody that selectively binds to abnormal endothelium that lines or composes neovascular tissue to a subject, (b) allowing non-specifically bound photosensitizing compound to clear from collateral tissues, (c) illuminating the neovascular tissue with light for a period of time sufficient to activate said photosensitizing compound thereby causing damage to neovascular tissue, but without impairing or destroying other tissue, wherein the subject is irradiated in or more sessions for a total period of 10 minutes with 400 mW/cm^2 of colliminated LED light

having a wavelength of 690nm for a total fluence of 240 Joules/cm^2, (2) a method to treat neovascular disease of the eye comprising the method steps of (a) administering a benzoporphyrin derivative conjugated to VEGF to a subject, (b) allowing non-specifically bound photosensitizing compound to clear from collateral tissues, (c) illuminating the neovascular tissue with light for a period of time sufficient to activate said photosensitizing compound thereby causing damage to neovascular tissue, but without impairing or destroying other tissue, wherein the subject is irradiated in one or more sessions for about 20 minutes with no more than 500 mW/cm^2 for a total fluence of illumination of about 600 Joules/cm^2, (3) a method to treat neovascular disease of the eye comprising the method steps of (a) administering a benzoporphyrin conjugated to anti-CEA antibody that selectively binds to abnormal endothelium that lines or composes neovascular tissue to a subject, (b) allowing non-specifically bound photosensitizing compound to clear from collateral tissues, (c) illuminating the neovascular tissue with light for a period of time sufficient to activate said photosensitizing compound thereby causing damage to neovascular tissue, but without impairing or destroying other tissue, wherein the subject is irradiated in or more sessions for approximately 1 hour with a radiant exposure of 250 mW/cm^2 for a total fluence of 900 Joules/cm^2. The specification defines a photosensitizing compound is a chemical compound which homes to one or more types of selected target cells and, when contacted by radiation, absorbs the light, which results in impairment or destruction of the target cells. Virtually any chemical compound that homes to a selected target and absorbs light may be used in this invention. Preferably, the chemical compound is nontoxic to the subject to which it is administered or is capable of being formulated in a nontoxic composition. Preferably, the chemical compound in its photodegraded form is also nontoxic. The disclosure further defines Photosensitive compounds include, but are *not limited to*, chlorins, bacteriochlorophylls, phthalocyanines, pophyrins, purpudns, merocyanines, psoralens, benzoporphyrin derivatives (BPD). Other compounds include indocyanine green (lCG); methylene blue; toluidine blue; texaphyrins; and *any other agent* that absorbs light in a range of 500 nm -1100 nm.

The specification does not teach how to make *any* "targeted photosensitizing compound" for the claimed method, much less treating neovascular disease comprising *any* combination of intensity of *any* light used for step of illuminating and any duration of illumination such as at least 4 minutes, at least 20 minutes, at least 1 hours and at least 24 hours to produce any total

fluence of irradiation such that the neovascular tissue is destroyed and the non-targeted tissue through which light passes through remains undamaged for the following reasons.

First, there is insufficient guidance as to the structure i.e., the amino acid sequence, chemical structure, and properties of any "targeted photosensitizing compound" in the claimed method. Based on the definition of the disclosure mentioned above, there is insufficient guidance as to which "other agent" that absorbs light in a range of 500nm-1100nm, would be useful for the claimed method without undue amount of experimentation.

Second, there is insufficient guidance as to the target such as the receptor, antigen, ligand, and antibody that binds to the undisclosed antigen on the abnormal endothelium that lines or composed neovascular tissue of the eye. Not only the structure of the any photosensitizing compound is not enabled, it is not clear which antigen on the abnormal endothelium is being targeted. With regard to binding pair, not only the specific ligand or receptor is not disclosed, there is insufficient guidance as to the "first component" and "second component" of any undisclosed bindable pair because the term "component" could be as little as one amino acid or it could be as much as 100 amino acids.

Stryer *et al* teach a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed relevant pages). In the absence of guidance as to the structure of the protein such as the antigen, the receptor, or the ligand, as well as specific component of said receptor and ligand, it is unpredictable which undisclosed antigen, receptor, ligand, and component of said receptor and component of said ligand would be effective for targeting any photosensitizing compound to the abnormal endothelium as a method for treating any disease.

With regard to antibody, because the specific antigen, receptor or ligand is not disclosed, the binding specificity of the antibody is questionable, in turn, and the targeted photosensitizing compound would bind specifically to the undisclosed antigen on the abnormal endothelium as a method to treat neovascular disease of the eye is not enabled.

Kuby *et al* teach that immunizing a peptide comprising a contiguous amino acid sequence of 8 amino acid residues or a protein derived from a full-length polypeptide may result in **antibody specificity** that differs from antibody specificity directed against the native full-length polypeptide. Given the indefinite number of undisclosed antigen, first component of any bindable pair and second component of any bindable pair such as receptor, ligand, antigen, and antibody to said ligand on the abnormal endothelium, it is unpredictable the binding specificity of

any undisclosed antibody to any antigen, ligand, receptor, or antigen would be useful for targeting the photosensitizing compound to the abnormal endothelium as a method to treat any neovascular disease of the eye. Given the indefinite number of "photosensitizing compound", "antigen", "bindable pair" of any ligand or receptor, antibody to any ligand, antibody to any receptor and whether said undisclosed ligand, receptor, antigen are expressed on the neovasculature tissue or abnormal endothelium, it is unpredictable which undisclosed ligand, receptor, antigen, antibody to said ligand or receptor would be effective for targeting the photosensitizing compound to the abnormal endothelium as a method to treat neovascular disease of the eye.

Third, even if the targeted photosensitizing compound is enabled, the light source, the combination of the intensity of light used for the step of illuminating and the duration of illumination to arrive at the total fluence are critical for the claimed method. In fact, the specification on page 10 discloses that "both intensity and duration must be limited to ovoid overtreating the subject". Given the lack of upper limit for the duration of illumination as set forth in claim 1 and 18-21, it is not clear if the claimed method as written is effective for treating neovascular disease without impairing or destroying other tissues. The recitation of "at least" 4 minutes (claim 18), "at least" 20 minutes (claim 19), "at least" 1 hour (claim 20) and "at least" 24 hours (claim 21) merely requires that lower limit of illumination be at least 4, 20, 1 and 24 hours, respectively. However, there is insufficient guidance for the intensity of the light used for the claimed method given the infinite number of undisclosed targeted photosensitizing compound.

It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions can result in substantially different pharmacological activities. Because of the lack of sufficient guidance and predicting which undisclosed targeted photosensitizing compound in which combination of light source, light intensity, and duration of illumination is effective for the claimed method, it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of the claimed method.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the

unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 8/25/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) the instant claims are not directed to any specific photosensitizing compound, but are directed to particular methods of using such compounds to treat neovascular disease of the eye. Therefore the structure of the photosensitizing compound is not relevant to patentability since any photosensitizing compound is contemplated for use in the claimed methods. The specification teaches that the photosensitizing compound absorbs light in the range of 500 nm - 1100 nm and that virtually any chemical compound that homes to a selected target and is activated by light may be used in the claimed method (see paragraph (0361). (2) The Level of skill in the art is high, (3) Many photosensitizing compounds were known at the time the application was submitted, including hematoporphyrins, porphyrins, chlorins, bacteriochlorins, benzoporphyrins, phthalocyanines, metallo-phthalocyanines and purpurines and their derivatives; naphthalocyanines, texaphyrins, porphycenes, platyrins and other extended tetrapyrroles (Kreimer-Birnbaum, Sem Hematol. 26(2): 157- 1 73 (1 989)). (4) The specification provides a detailed amount of direction and guidance for selection of a photosensitizing compound that is encompassed in the claims. The specification provides several working examples illustrating exactly how to use various photosensitizing compounds in the claimed methods for treating neovascular disease of the eye (examples 1-4).

However, the specification does not teach how to make *any* "targeted photosensitizing compound" for the claimed method, much less treating neovascular disease comprising *any* combination of intensity of *any* light used for step of illuminating and any duration of illumination such as at least 4 minutes, at least 20 minutes, at least 1 hours and at least 24 hours to produce any total fluence of irradiation such that the neovascular tissue is destroyed and the non-targeted tissue through which light passes through remains undamaged for the following reasons.

First, there is insufficient guidance as to the structure i.e., the amino acid sequence, chemical structure, and properties of any "targeted photosensitizing compound" in the claimed method. Based on the definition of the disclosure mentioned above, there is insufficient guidance as to which **"other agent"** that absorbs light in a range of 500nm-1100nm, would be useful for the claimed method without undue amount of experimentation. Second, there is insufficient

guidance as to the target such as the receptor, antigen, ligand, and antibody that binds to the undisclosed antigen on the abnormal endothelium that lines or composed neovascular tissue of the eye. Not only the structure of the any photosensitizing compound is not enabled, it is not clear which antigen on the abnormal endothelium is being targeted. Third, even if the targeted photosensitizing compound is enabled, the light source, the combination of the intensity of light used for the step of illuminating and the duration of illumination to arrive at the total fluence are critical for the claimed method. In fact, the specification on page 10 discloses that "both intensity and duration must be limited to ovoid overtreating the subject". Given the lack of upper limit for the duration of illumination as set forth in claim 1 and 18-21, it is not clear if the claimed method as written is effective for treating neovascular disease without impairing or destroying other tissues. The recitation of "at least" 4 minutes (claim 18), "at least" 20 minutes (claim 19), "at least" 1 hour (claim 20) and "at least" 24 hours (claim 21) merely requires that lower limit of illumination be at least 4, 20, 1 and 24 hours, respectively. However, there is insufficient guidance for the intensity of the light used for the claimed method given the infinite number of undisclosed targeted photosensitizing compound in any combination of light intensity and duration of illumination. It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions can result in substantially different pharmacological activities. Because of the lack of sufficient guidance and predicting which undisclosed targeted photosensitizing compound in which combination of light source, light intensity, and duration of illumination is effective for the claimed method, it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of the claimed method.

6. Claims 1-6, 11-12, 16-24, 36, and 38-41 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of method to treat neovascular disease of the eye as set forth in claims 19, 11-12, 16-24, 36, and 38-41.

The specification discloses only (1) a method to treat neovascular disease of the eye comprising the method steps of (a) administering a verteporfin conjugated anti-ED-B of fibronectin antibody that selectively binds to abnormal endothelium that lines or composes

neovascular tissue to a subject, (b) allowing non-specifically bound photosensitizing compound to clear from collateral tissues, (c) illuminating the neovascular tissue with light for a period of time sufficient to activate said photosensitizing compound thereby causing damage to neovascular tissue, but without impairing or destroying other tissue, wherein the subject is irradiated in or more sessions for a total period of 10 minutes with 400 mW/cm^2 of colliminated LED light having a wavelength of 690nm for a total fluence of 240 $Joules/cm^2$, (2) a method to treat neovascular disease of the eye comprising the method steps of (a) administering a benzoporphyrin derivative conjugated to VEGF to a subject, (b) allowing non-specifically bound photosensitizing compound to clear from collateral tissues, (c) illuminating the neovascular tissue with light for a period of time sufficient to activate said photosensitizing compound thereby causing damage to neovascular tissue, but without impairing or destroying other tissue, wherein the subject is irradiated in one or more sessions for about 20 minutes with no more than 500 mW/cm^2 for a total fluence of illumination of about 600 $Joules/cm^2$, (3) a method to treat neovascular disease of the eye comprising the method steps of (a) administering a benzoporphyrin conjugated to anti-CEA antibody that selectively binds to abnormal endothelium that lines or composes neovascular tissue to a subject, (b) allowing non-specifically bound photosensitizing compound to clear from collateral tissues, (c) illuminating the neovascular tissue with light for a period of time sufficient to activate said photosensitizing compound thereby causing damage to neovascular tissue, but without impairing or destroying other tissue, wherein the subject is irradiated in or more sessions for approximately 1 hour with a radiant exposure of 250 mW/cm^2 for a total fluence of 900 $Joules/cm^2$.

With the exception of the specific method to treat neovascular disease of the eye using the specific target photosensitizing compound in the specific combination of light intensity and duration of illumination to produce the total fluence of illumination without impairing or destroying other tissue mentioned above, there is insufficient written description about the structure associated with function of *any* "targeted photosensitizing compound" for the claimed method. Further, there is inadequate written description about the method step wherein a combination of any intensity of light use for the step of illuminating and any duration of illumination such as at 4 minutes, at least 20 minutes, at least 1 hour and at least 24 hours along with any undisclosed target photosensitizing compound. In fact, the specification on page 10 discloses that "*both intensity and duration must be limited to ovoid overtreating the subject*". Given the lack of upper limit for the duration of illumination as set forth in claim 1 and 18-21, it

is not clear if the claimed method as written is effective for treating neovascular disease without impairing or destroying other tissues. The recitation of "at least" 4 minutes (claim 18), "at least" 20 minutes (claim 19), "at least" 1 hour (claim 20) and "at least" 24 hours (claim 21) merely requires that lower limit of illumination be at least 4, 20, 1 and 24 hours, respectively. However, there is insufficient guidance for the intensity of the light used for the claimed method given the infinite number of undisclosed targeted photosensitizing compound in any combination of light intensity and duration of illumination. Finally, the method step of allowing non-specifically bound photosensitizing compound to clear from collateral tissues is missing in the claims which clearly required by the disclosure (See examples 1-4).

Further, given the lack of an additional species of photosensitizing compound in combination with any intensity of light used for the step of illuminating and any duration of illumination for the claimed method, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 8/25/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) claim 1 is directed to a method of photodynamic therapy to treat neovascular disease of the eye that includes administering a targeted photosensitizing compound that selectively binds to abnormal endothelium that lines or composes neovasculature tissue. (2) there is no indication in the art that there is substantial variation among members of photosensitizing compound of the genus. (3) The specification teaches that those of skill in the art recognize common elements among photosensitizing compounds. For example, the specification teaches that the chemical is nontoxic to the subject prior to irradiation or in its photodegraded form, and absorbs light in a range of 500-1 100 nm (paragraph (0361), whereby the chemical is activated and generates singlet oxygen and other reactive species that have biological effects resulting in damage to the endothelial membranes and ultimately to clotting the neovasculature (see paragraph (0051). (4) The specification provides a representative number of examples of receptors, antigens, ligands and antibodies of the binding pair explicitly (including

VEGF, VEGF receptor, αvβ3 integrin receptor, CEA antigen, antibody to the extra-domain B of fibronectin, such as L19, antibody to αvβ3, such as LM6O9, antibody to CEA, and bispecific antibody construct that is a combination of ligand and receptor (see paragraphs [021], [043], [044] and [061]) and implicitly (such as antibodies and antibody fragments that bind to abnormal vascular endothelial receptors, and antibodies and antibody fragments that bind to upregulated vascular endothelial receptors).

In response, other than the specific method to treat neovascular disease of the eye using the specific target photosensitizing compound in the specific combination of light intensity and duration of illumination to produce the total fluence of illumination without impairing or destroying other tissue mentioned above, there is insufficient written description about the structure associated with function of *any* "targeted photosensitizing compound" for the claimed method. Further, there is inadequate written description about the method step wherein a combination of any intensity of light use for the step of illuminating and any duration of illumination such as at 4 minutes, at least 20 minutes, at least 1 hour and at least 24 hours along with any undisclosed target photosensitizing compound. In fact, the specification on page 10 discloses that "both intensity and duration must be limited to ovoid overtreating the subject". Given the lack of upper limit for the duration of illumination as set forth in claim 1 and 18-21, it is not clear if the claimed method as written is effective for treating neovascular disease without impairing or destroying other tissues. The recitation of "at least" 4 minutes (claim 18), "at least" 20 minutes (claim 19), "at least" 1 hour (claim 20) and "at least" 24 hours (claim 21) merely requires that lower limit of illumination be at least 4, 20, 1 and 24 hours, respectively. However, there is insufficient guidance for the intensity of the light used for the claimed method given the infinite number of undisclosed targeted photosensitizing compound in any combination of light intensity and duration of illumination. Finally, the method step of allowing non-specifically bound photosensitizing compound to clear from collateral tissues is missing in the claims which clearly required by the disclosure (See examples 1-4).

In response to applicant's argument that there is no indication in the art that there is substantial variation among members of photosensitizing compound of the genus, there is inadequate written description about the "**other agent**" that absorbs light in a range of 500nm-1100nm, in combination with the step wherein the intensity is any intensity, and any duration of illumination would be useful causing damage to neovascular tissue but without impairing or destroying other tissue for the claimed method.

In response to applicant's argument that the specification provides a representative number of examples of targeted photosensitizing compound for the claimed method, it is noted that these photosensitizing compound such as receptors, antigens, ligands and antibodies of the binding pair explicitly (including VEGF, VEGF receptor, αvβ3 integrin receptor, CEA antigen, antibody to the extra-domain B of fibronectin, such as L19, antibody to αvβ3, such as LM6O9, antibody to CEA are exemplified embodiments in a specific combination of light intensity and duration to achieve the specific total fluence of illumination such that the neovascular tissue is destroyed and the non-targeted tissue through which the light passes remains undamaged. Further, the method step of allowing non-specifically bound photosensitizing compound to clear from collateral tissues is missing in the claims which clearly required by the disclosure (See examples 1-4).

7. Claims 1-9, 11-12, 16-24, 36, and 38-41 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

"A method ....**total fluence of irradiation** ....remains undamaged" in Claims 1-9, 11-12, 16-24, 36, and 38-41 represents a departure from the specification and the claims as originally filed. The passages pointed out by applicant in the amendment filed 8/25/03 do not provide a clear support for the said phrase.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1, 3, 4, 6, 18-21, 36, and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No 5,756,541 (May 1998; PTO 1449).

The '541 patent teaches a method to treat neovascular disease of the eye such as age-related macular degeneration comprising administering a photosensitizing compound such as chlorine and green porphyrin (See claim 6 of '541, column 2, line 15, Fig 1, column 35-60, in particular) coupled to a specific binding ligand such as antibody that binds to the target ocular

tissue (See column 3, lines 29-31, column 4, lines 11-13, in particular). The reference method further comprises the step of illuminating the neovasculature tissue with laser light for a period of time such as 90 second to cause damage to the neovasculature tissue without impairing or destroying other tissue (See column 5, lines 10-12 and lines 21, claims of '541 patent, in particular). The reference method wherein the reference targeted photosensitizing compound is formulated in liposome since it selectively delivers the reference compound to the low-density lipoprotein component of the plasma of neovascular tissue (See column 3, lines 40-45, in particular). The reference method wherein the photosensitizing compound is illuminated for about 1 minutes to about 2 hours, and more preferably at least 10-25 minutes (See column 5, lines 2-4, in particular). The reference irradiance varies from about 150 to 900 mW/cm2 or a fluence of 50 to 150 j/cm2 (See column 5, lines 47-48, in particular). Claim 36 is included in this rejection because the instruction to a person to conduct the claimed method at the time the invention was made is within the teachings of the '541 patent. Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 8/25/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) Strong et al. does not disclose a method to treat neovascular disease of the eye that includes as a step selecting a combination of an intensity of light used for the step of illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged . Strong et al. does not disclose any significance of the parameters of light intensity and/or duration of irradiation, nor is there any disclosure on the selection of a combination of these parameters in further combination with the use of a targeted photosensitizer compound for use in methods of photodynamic therapy to achieve target tissue destruction without damage to non-target tissue. (2) because strong et al discloses a fluence between 50-200 J/cm2, Strong et al does not disclose illuminating the photosensitized neovasculature for at least 20 minutes, or at least 1 hour or at least 24 hours.

In response, it is noted that the amended claim 1 does NOT recite the specific combination of an intensity of light used for the step of illuminating and the specific duration of illumination to produce the specific total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged. Further, Strong et al (the '541 patent here after) discloses that the duration of light irradiation depends on

the fluence desired (col. 5, lines 5-8) such as 50 to 150 j/cm2 (See column 5, lines 47-48, in particular) and for the duration of illumination such as about 1 minutes to about 2 hours, and more preferably at least 10-25 minutes (See column 5, lines 2-4, in particular). The '541 patent teaches a method to treat neovascular disease of the eye such as age-related macular degeneration comprising administering a photosensitizing compound such as chlorine and green porphyrin (See claim 6 of '541, column 2, line 15, Fig 1, column 35-60, in particular) coupled to a specific binding ligand such as antibody that binds to the target ocular tissue (See column 3, lines 29-31, column 4, lines 11-13, in particular). Given that the claimed method steps are the same as that of the prior art, the outcome of the reference method appears to be the same outcome as that of the claimed method. Since the Patent Office does not have the facilities for examining and comparing the method of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977).

In response to Applicants' argument that Strong et al does not disclose illuminating the photosensitized neovasculature for at least 20 minutes, or at least 1 hour or at least 24 hours, the '541 patent teaches the duration of irradiation depends on the fluence desired (column 5, lines 5-6, in particular). Further, the amended claim 1 does not recite the specific total fluence and the specific light source. It is within the purview of one ordinary skill in the photodynamic art to illuminate the neovascular tissue for the duration such as at least 20 minutes, at least 1 hours or at least 24 hours based on the fluence desired as taught by the '541 patent. Claim 22 has been dropped from this rejection because the '541 patent does not teach the parameter of a total fluence of light irradiation from between about 240 J/cm^2 to about 900 J/cm^2.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1, 2, 11-12 and 38-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,756,541 (May 1998; PTO 1449) in view of Boulton *et al* (Br J Opthlalmol 82: 561-568, 1998; PTO 892), Blaauwgeers *et al* (Am J Pathology 155(2): 421-428, 1999; PTO 892), Klyashchitsky *et al* (J of Controlled Release 29(1-2): 16-16, 1994; PTO 892) and Prewett *et al* (Cancer Res 59: 5209-18, 1999; PTO 892).

The teachings of the '541 patent have been discussed supra. The '541 patent further teaches the targeted photosensitizing compound is formulated in liposome since it selectively delivers the reference compound to the low-density lipoprotein component of the plasma of neovascular tissue (See column 3, lines 40-45, in particular).

The claimed invention in claim 2 differs from the teachings of the reference only that the method wherein the light is non-laser light.

The claimed invention in claim 11 differs from the teachings of the reference only that the targeted photosensitizing compound is bound to a first component of a bindable pair such as VEGF receptor antibody and wherein a second component of the bindable pair is VEGF present on abnormal endothelium.

The claimed invention in claim 12 differs from the teachings of the reference only that the targeted photosensitizing compound is incorporated into a liposomal preparation.

The claimed invention in claim 38 differs from the teachings of the reference only that the targeted photosensitizing compound is conjugated to an antibody that binds to a VEGF receptor.

The claimed invention in claim 39 differs from the teachings of the reference only that the targeted photosensitizing compound is conjugated to VEGF.

The claimed invention in claim 40 differs from the teachings of the reference only that the targeted photosensitizing compound is conjugated to VEGF receptor.

Boulton *et al* teach VEGF plays a role in neovascularization in diabetic retinopathy and antibody to VEGF detects VEGF in endothelial cell in the retinal or choroidal of diabetic retina (see Abstract, Table 1, page 563, column 1, first paragraph, in particular). Boulton *et al* teach VEGF binds to VEGF receptors on endothelial cells such as inner retina (See page 566, column 2, first full paragraph, in particular).

Blaauwgeers *et al* teach VEGF receptor such as VEGFR-2 or KDR and VEGFR-3 (flt-4) are localized to the choriodcapillaris (CC) endothelium facing the retinal pigment epithelium layer whereas VEGFR-1 is found in the inner CC on other choroidal vessel (See abstract, in

particular). Blaauwgeers *et al* teach that unregulated VEGF secretion by RPE plays a role in neovascularization.

Klyashchitsky *et al* teach photodynamic therapy (PDT) is based on the ability of porphyrins and other photosensitizers to be accumulated preferentially in cells such as tumors and to generate singlet oxygen when activated by visible light (See abstract, in particular). Klyashchitsky *et al* further teach that targeting molecule such as antibody that is specific for antigen or the receptor is efficient and useful for delivery of PDT selectively to the tumor cells (See abstract, in particular).

Prewett *et al* teach antibody such as DC101 that binds specifically to Flk-1/KDR VEGF receptor and the reference antibody is useful for inhibits angiogenesis (See entire document, abstract, Fir 2, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody that is conjugated to the photosensitizer as taught by the '541 patent for the antibody to the VEGF receptor as taught by Prewett *et al* or the VEGF as taught by Boulton *et al* or the VEGF receptor as taught by Boulton et al and Blaauwgeers *et al* for targeting the photosensitizing compound to treat neovascular disease as taught by the '541 patent and Klyashchitsky *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Klyashchitsky *et al* teach that targeting molecule such as antibody that is specific for antigen or receptor is efficient and useful for selective delivery of PDT to the site of interest (See abstract, in particular). Prewett *et al* teach antibody such as DC101 that binds specifically to the Flk-1/KDR VEGF receptor and the reference antibody is useful for inhibits angiogenesis (See entire document, abstract, Fir 2, in particular). Blaauwgeers *et al* teach VEGF receptor such as VEGFR-2 or KDR and VEGFR-3 (flt-4) are localized to the choriocapillaries (CC) endothelium facing the retinal pigment epithelium layer whereas VEGFR-1 is found in the inner CC on other choroidal vessel (See abstract, in particular). Boulton *et al* teach that VEGF binds to VEGF receptors on endothelial cells such as inner retina play a role in neovascularization in diabetic retinopathy (See page 566, column 2, first full paragraph, abstract, in particular). The '541 patent teaches that administering a photosensitizing compound such as chlorine and green porphyrin (See claim 6 of '541, column 2, line 15, Fig 1, column 35-60, in particular) coupled to a specific

binding ligand such as antibody that binds to the target ocular tissue (See column 3, lines 29-31, column 4, lines 11-13, in particular) is useful for treating neovascular disease of the eye such as age-related macular degeneration (See claim 6 of '541, column 2, line 15, Fig 1, column 35-60, in particular).

Applicants' arguments filed 8/25/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) Strong et al. does not disclose a method to treat neovascular disease of the eye that includes as a step selecting a combination of an intensity of light used for the step of illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged . Strong et al. does not disclose any significance of the parameters of light intensity and/or duration of irradiation, nor is there any disclosure on the selection of a combination of these parameters in further combination with the use of a targeted photosensitizer compound for use in methods of photodynamic therapy to achieve target tissue destruction without damage to non-target tissue. (2) because strong et al discloses a fluence between 50-200 J/cm2, Strong et al does not disclose illuminating the photosensitized neovasculature for at least 20 minutes, or at least 1 hour or at least 24 hours. (3) Boulton et al, Klyashchitsky et al, Prewett et al do not cure these defects. (4) The rejection is based on improper hindsight. (5) The Examiner's attention is directed to co-owned Patent No 6,602,274, based on USSN 09/271,575. The issue claims in the co-owned patent, which has the same inventive entity, are directed to a generic method of photodynamic therapy. (5) Strong et al does not teach non-laser light (claim 2) or binding the photsensitizer to a first member of a binding pair (claim 11) or incorporation of the targeted photosensitizing compound into a liposomal preparation.

As discussed above and below, it is noted that the amended claim 1 does NOT recite the specific combination of an intensity of light used for the step of illuminating and the specific duration of illumination to produce the specific total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged. Further, Strong et al (the '541 patent here after) discloses that the duration of light irradiation depends on the fluence desired (col. 5, lines 5-8) such as 50 to 150 j/cm2 (See column 5, lines 47-48, in particular) and for the duration of illumination such as about 1 minutes to about 2 hours, and more preferably at least 10-25 minutes (See column 5, lines 2-4, in particular). The

'541 patent teaches a method to treat neovascular disease of the eye such as age-related macular degeneration comprising administering a photosensitizing compound such as chlorine and green porphyrin (See claim 6 of '541, column 2, line 15, Fig 1, column 35-60, in particular) coupled to a specific binding ligand such as antibody that binds to the target ocular tissue (See column 3, lines 29-31, column 4, lines 11-13, in particular). Given that the claimed method steps are the same as that of the prior art, the outcome of the reference method appears to be the same outcome as that of the claimed method. Since the Patent Office does not have the facilities for examining and comparing the method of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977).

In response to Applicants' argument that Strong et al does not disclose illuminating the photosensitized neovasculature for at least 20 minutes, or at least 1 hour or at least 24 hours, the '541 patent teaches the duration of irradiation depends on the fluence desired (column 5, lines 5-6, in particular). Further, the amended claim 1 does not recite the specific total fluence and the specific light source. It is within the purview of one ordinary skill in the photodynamic art to illuminate the neovascular tissue for the duration such as at least 20 minutes, at least 1 hours or at least 24 hours based on the fluence desired as taught by the '541 patent. Claim 22 has been dropped from this rejection because the '541 patent does not teach the parameter of a total fluence of light irradiation from between about 240 J/cm^2 to about 900 J/cm^2.

In response to applicant's argument that the rejection is based on improper hindsight, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. In re McLaughlin, 170 USPQ 209 (CCPA 1971).

In response to applicant's argument that co-owned patent, which has the same inventive entity, are directed to a generic method of photodynamic therapy, every patent is examined on its own merit.

In response to Applicants' argument that Strong et al does not non-laser light, Klyashchitsky *et al* teach photodynamic therapy (PDT) is based on the ability of porphyrins and other photosensitizers to be accumulated preferentially in cells such as tumors and to generate

singlet oxygen when activated by visible light, which is a non-laser light (See abstract, in particular).

In contrast to Applicants' argument that Strong et al does not teach binding the photsensitizer to a first member of a binding pair (claim 11) or incorporating the targeted photosensitizing compound into a liposomal preparation (claim 12), the '541 patent teaches photoactive agent is formulated so as to provide an effective concentration to the target ocular tissue such as coupled to a specific binding ligand (first member) which may bind to a specific surface component of the target ocular tissue (second member) (See column 3, lines 28-30, in particular). The '541 patent further teaches the formulation include liposomes and liposomal compositions are particularly preferred (See column 3, lines 40-41, in particular). However, the '541 patent does not teach the specific binding pair such as anti-VEGFR (first member) that binds to the VEGF (second member) on abnormal endothelium. Boulton *et al* teach VEGF plays a role in neovascularization in diabetic retinopathy and antibody to VEGF detects VEGF in endothelial cell in the retinal or choroidal of diabetic retina (see Abstract, Table 1, page 563, column 1, first paragraph, in particular). Boulton *et al* teach VEGF binds to VEGF receptors on endothelial cells such as inner retina (See page 566, column 2, first full paragraph, in particular).

Blaauwgeers *et al* teach VEGF receptor such as VEGFR-2 or KDR and VEGFR-3 (flt-4) are localized to the choriocapillaries (CC) endothelium facing the retinal pigment epithelium layer whereas VEGFR-1 is found in the inner CC on other choroidal vessel (See abstract, in particular). Blaauwgeers *et al* teach that unregulated VEGF secretion by RPE plays a role in neovascularization.

Klyashchitsky *et al* teach photodynamic therapy (PDT) is based on the ability of porphyrins and other photosensitizers to be accumulated preferentially in cells such as tumors and to generate singlet oxygen when activated by visible light (See abstract, in particular). Klyashchitsky *et al* further teach that targeting molecule such as antibody that is specific for antigen or the receptor is efficient and useful for delivery of PDT selectively to the tumor cells (See abstract, in particular).

Prewett *et al* teach antibody such as DC101 that binds specifically to Flk-1/KDR VEGF receptor and the reference antibody is useful for inhibits angiogenesis (See entire document, abstract, Fir 2, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody as taught by the '541 patent for the antibody to the

VEGF receptor as taught by Prewett *et al* to target the photosensitizing compound such as chlorine and green porphyrin as taught by the '541 patent and Klyashchitsky *et al* to the neovascular tissue of the retina as taught by Boulton *et al* and Blaauwgeers *et al* for a method to treat neovascular disease of the eye as taught by the'541 patent, Boulton *et al*, Blaauwgeers *et al* and Prewett *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Klyashchitsky *et al* teach that targeting molecule such as antibody that is specific for antigen or receptor is efficient and useful for selective delivery of PDT to the site of interest (See abstract, in particular). Prewett *et al* teach antibody such as DC101 that binds specifically to the Flk-1/KDR VEGF receptor and the reference antibody is useful for inhibits angiogenesis (See entire document, abstract, Fir 2, in particular). Blaauwgeers *et al* teach VEGF receptor such as VEGFR-2 or KDR and VEGFR-3 (flt-4) are localized to the choriocapillaries (CC) endothelium facing the retinal pigment epithelium layer whereas VEGFR-1 is found in the inner CC on other choroidal vessel (See abstract, in particular). Boulton *et al* teach that VEGF binds to VEGF receptors on endothelial cells such as inner retina play a role in neovascularization in diabetic retinopathy (See page 566, column 2, first full paragraph, abstract, in particular). The '541 patent teaches that administering a photosensitizing compound such as chlorine and green porphyrin (See claim 6 of '541, column 2, line 15, Fig 1, column 35-60, in particular) coupled to a specific binding ligand such as antibody that binds to the target ocular tissue (See column 3, lines 29-31, column 4, lines 11-13, in particular) is useful for treating neovascular disease of the eye such as age-related macular degeneration (See claim 6 of '541, column 2, line 15, Fig 1, column 35-60, in particular).

12. Claims 1 and 16-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,756,541 (May 1998; PTO 1449) in view of US Pat 6,051,230 (April 2000, PTO 892).

The teachings of the '541 patent have been discussed supra. The '541 patent further teaches the targeted photosensitizing compound is formulated in liposome since it selectively delivers the reference compound to the low-density lipoprotein component of the plasma of neovascular tissue (See column 3, lines 40-45, in particular).

The claimed invention in claim 16 differs from the teachings of the reference only that the method wherein the targeting photosensitizing compound is bound to a bi-specific antibody construct that further comprises both a ligand component and a receptor component.

The claimed invention in claim 17 differs from the teachings of the reference only that the method wherein the targeted photosensitizing compound is incorporated into a liposomal preparation.

The '230 patent teaches various antibodies that bind specifically to VEGF (See column 83, lines 39-67 and column 84, Table X, in particular), various bispecific antibodies as well as a method of making various bispecific antibodies that comprise two chosen antibodies one desired such as VEGF receptor and a ligand component such as VEGF for targeting to endothelial cells of vascularization (See column 29, lines 20-42, claim 46 of '230 patent, in particular). The '230 patent teaches that bispecific antibodies carrying diagnostic or therapeutic agents are targeted to the vasculature through recognition of VEGF and/or through receptor binding on endothelial cells (See abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody as taught by the '541 patent for the bispecific antibody that binds to the VEGF and the VEGF receptor as taught by the '230 patent for targeting the photosensitizing compound such as chlorine and green porphyrin as taught by the '541 patent to the neovasculature tissue for treating neovascular disease of the eye. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '230 patent teaches bispecific antibodies carrying diagnostic or therapeutic agents are targeted to the vasculature through recognition of VEGF and/or through receptor binding on endothelial cells (See abstract, in particular).

Applicants' arguments filed 8/25/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) Strong et al. does not disclose a method to treat neovascular disease of the eye that includes as a step selecting a combination of an intensity of light used for the step of illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged . Strong et al. does not disclose any significance of the

parameters of light intensity and/or duration of irradiation, nor is there any disclosure on the selection of a combination of these parameters in further combination with the use of a targeted photosensitizer compound for use in methods of photodynamic therapy to achieve target tissue destruction without damage to non-target tissue. (2) because strong et al discloses a fluence between 50-200 J/cm2, Strong et al does not disclose illuminating the photosensitized neovasculature for at least 20 minutes, or at least 1 hour or at least 24 hours. (3) the bi-specific antibody construct of Thorpe includes two ligand components (each of which recognize a different cell surface antigen). Thorpe et al does not teach or suggest a bispecific antibody construct that includes both a ligand component and a receptor component.

As discussed above and below, it is noted that the amended claim 1 does NOT recite the specific combination of parameters such as an intensity of light used for the step of illuminating and the specific duration of illumination to produce the specific total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged. Further, Strong et al (the '541 patent here after) discloses that the duration of light irradiation depends on the fluence desired (col. 5, lines 5-8) such as 50 to 150 j/cm2 (See column 5, lines 47-48, in particular) and for the duration of illumination such as about 1 minutes to about 2 hours, and more preferably at least 10-25 minutes (See column 5, lines 2-4, in particular). The '541 patent teaches a method to treat neovascular disease of the eye such as age-related macular degeneration comprising administering a photosensitizing compound such as chlorine and green porphyrin (See claim 6 of '541, column 2, line 15, Fig 1, column 35-60, in particular) coupled to a specific binding ligand such as antibody that binds to the target ocular tissue (See column 3, lines 29-31, column 4, lines 11-13, in particular). Given that the claimed method steps are the same as that of the prior art, the outcome of the reference method appears to be the same outcome as that of the claimed method. Since the Patent Office does not have the facilities for examining and comparing the method of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977).

In response to Applicants' argument that Strong et al does not disclose illuminating the photosensitized neovasculature for at least 20 minutes, or at least 1 hour or at least 24 hours, the '541 patent teaches the duration of irradiation depends on the fluence desired (column 5, lines 5-6, in particular). Further, the amended claim 1 does not recite the specific total fluence and the specific light source. It is within the purview of one ordinary skill in the photodynamic art to

illuminate the neovascular tissue for the duration such as at least 20 minutes, at least 1 hours or at least 24 hours based on the fluence desired as taught by the '541 patent. Claim 22 has been dropped from this rejection because the '541 patent does not teach the parameter of a total fluence of light irradiation from between about 240 J/cm^2 to about 900 J/cm^2.

In contrast to applicant's assertion that Thorpe ('230 patent) does not teach or suggest a bispecific antibody construct that includes both a ligand component and a receptor component, Thrope et al teach a bispecific antibody that binds to a ligand component such as fibroblast growth factor and a second component such as fibroblast growth factor receptor (See claim 49 of '230 patent, column 29, lines 20-25, in particular).

In response to Applicants' argument that Thorpe et al. does not teach or suggest treating neovascular disease using a photosensitizing compound, nor does the reference teach or suggest a targeted photosensitizing compound that selectively binds to abnormal endothelium, One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., Inc. , 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). See MPEP 2145. In instant case, the '541 patent teaches a method to treat neovascular disease of the eye such as age-related macular degeneration comprising administering a targeted photosensitizing compound such as chlorine and green porphyrin (See claim 6 of '541, column 2, line 15, Fig 1, column 35-60, in particular) coupled to a specific binding ligand such as antibody that binds to the target ocular tissue (See column 3, lines 29-31, column 4, lines 11-13, in particular). The reference method further comprises the step of illuminating the neovasculature tissue with laser light for a period of time such as 90 second to cause damage to the neovasculature tissue without impairing or destroying other tissue (See column 5, lines 10-12 and lines 21, claims of '541 patent, in particular).

13. Claims 22-24 are free of prior art.

14. No claim is allowed.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 8:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist (customer service) whose telephone number is (703) 872-9305.

17. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The IFW official Fax number is (703) 872-9306.

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
January 12, 2004

Christina Chan

CHRISTINA CHAN
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